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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/836,477	04/18/2001	Brendan Larder	VIP0011	8810

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EXAMINER	
CLOW, LORI A	

ART UNIT	PAPER NUMBER
1631	

DATE MAILED: 08/13/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/836,477	LARDER ET AL.	
	Examiner	Art Unit	
	Lori A. Clow, Ph.D.	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *13 May 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-32 and 39-42* is/are pending in the application.

4a) Of the above claim(s) *33-38* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-32 and 39-42* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *12 June 2002*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's election with traverse of Group I, claims 1-27 and 39-42 on 13 May 2004 is acknowledged.

Applicant states that at least Group I and II should be rejoined into one group, as they are so closely related. The Examiner agrees and is hereby rejoining claims 28-32 for prosecution on the merits.

The Examiner disagrees with the assessment that Groups III, IV, and V should also be examined or should be placed in one Group. For the reasons set forth in the Restriction Requirement, these groups constitute distinct inventions. The requirement is still deemed proper and therefore made FINAL.

Claims 1-32 and 39-42 are now currently pending. Applicant is reminded to cancel claims to non-elected inventions.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-6, 8-10, 14-32, and 39-42 are rejected under 35 U.S.C. 112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

Claims 1-6, 8-10, 14-32, and 39-42 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a method of determining a phenotype of a biological sample containing HIV, does not reasonably provide enablement for a method of determining any known phenotype from a mutation pattern phenotype. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use the invention commensurate in scope with these claims.

In *In re Wands* (8 USPQ2d 1400 (CAFC 1988)) the CAFC considered the issue of enablement in molecular biology. The CAFC summarized eight factors to be considered in a determination of "undue experimentation". These factors include: (a) the quantity of experimentation necessary; (b) the amount of direction or guidance presented; (c) the presence or absence of working examples; (d) the nature of the invention; (e) the state of the prior art; (f) the relative skill of those in the art; (g) the predictability of the art; and (h) the breadth of the claims.

In considering the factors for the instant claims:

a) In order to practice the claimed invention one of skill in the art must use the steps as set forth in the claims to practice the method of predicting a phenotype of a biological sample. For the reasons discussed below, there would be an unpredictable amount of experimentation required to practice the claimed invention.

b), c) The specification provides guidance for analyzing HIV samples for mutations that are indicative of a resistance to HIV therapy.

d) The invention is drawn to methods of predicting phenotypes of any unknown sample by correlation of mutation data.

e), g) In the art of pathogen resistance (as an example of phenotype), it is well known that every pathogen is very different, and does not respond the same way to every agent. Agents effective against a bacterial infection are not effective against a viral infection. Further, not all pathogens have been sequenced, and for those that have, those sequences are ever evolving in the face of today's antipathogenic agents. One of skill in the art would not be able to pick any pathogen and any agent and then look to the specification for how to design and practice the invention as claimed.. The specification does not provide information as to the important genetic sequences of every pathogen, and how those sequences or their changes are related to resistance to various agents. The specification does not provide training sets which are applicable to any or all known mutations of any or all pathogens that are related to resistance such that one of skill in the art would be able to practice the prediction of resistance on a new species or sequence of a pathogen. .

f) The skill of those in the art of molecular biology is high.

g) The claims are broad because they are drawn to methods of predicting whether any pathogen or variant of a pathogen would be resistant to any agent (phenotype).

The skilled practitioner would first turn to the instant specification for guidance to practice methods predicting such resistance. However, the instant specification does not provide specific guidance to practice these embodiments. As such, the skilled practitioner would turn to the prior art for such guidance, however, the prior art shows that the pathogens of the world are extremely diverse, having wildly divergent replication and infection strategies. The sequences of all pathogens are not so similar that direct correlations can already be made, and much is unknown about how certain mutations affect pathogen resistance. Finally, said practitioner

would turn to trial and error experimentation to determine what pathogen to test, what the genetic sequences of those pathogens are, how they correlate to resistance to a particular agent. After such lengthy experiments, then one would need to prepare test sets to determine the accuracy of the findings and make predictions. Such studies would have to be repeated for every particular agent, and every particular pathogen. Such represents undue experimentation.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later

invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-13, 16-18, 23-28, and 39-42 are rejected under 35 U.S.C. 103(a) as being unpatentable over Harrigan et al. (AIDS (1999) Vol. 13, No. 14, pages 1863-1871 in view of Ioannidis et al. (American Journal of Epidemiology (1998) Vol. 147, No. 5, pages 464-471.

Harrigan et al. teach a baseline HIV drug resistance profile for predicting response to ritonavir and saquinavir protease inhibitor therapy.

In regard to claims 1 and 28, Harrigan et al. teach that Resistance to 10 different antiviral agents was assessed by both phenotype and genotype. The resistance inferred from the viral genotype was similar to measured phenotypic resistance for both retinavir and saquinavir (page 1, paragraph 1 and 2). The collection of genotypic and phenotypic data allows correlation to be made with each other. Data were obtained from baseline genotypes using virtual phenotype, assignments of resistance, non-resistant/sensitive or resistant-possible of the Vircogen software (see Tables 3 and 4).

In regard to claims 2 and 40, resistance was measured for 10 different antiviral agents.

In regard to claim 3, resistance was measured to ritonavir and to saquinavir (page 1, paragraph 2).

In regard to claim 4, plasma samples were used (page 1863, paragraph 2).

In regard to claims 5-7 and 9-12, HIV drug resistance was measured.

In regard to claims 8, 13,16, and 18 protease codons were assessed for multiple mutations (page 5).

In regard to claims 23 and 24, the amount of drug required to inhibit viral production by 50% (IC50) was determined by an MIT dye reduction assay in MT-4 cells. The IC50 is compared to control laboratory, wild-type, virus. An increase greater that four-fold was defined as resistant.

In regard to claims 25-27 and 41-42 Harrigan et al. teaches that the HIV method for drug resistance creates a profile for clinical use.

Harrigan et al. do not specifically teach searching a relational database. However, Ioannidis et al. do teach the use of neural networks to model complex immunogenetic associations of disease. In particular, HLA data on class I and II alleles and TAP variants from two cohort studies of HIV seroconverters were used to train a neural network for use in establishing the progression of HIV in the set or patients.

Therefore, it would have been prima facie obvious to one of skill in the art at the time of the invention to employ the neural network of Ioannidis et al. for the assessment of predicting drug resistance of HIV, as is done by Harrigan et al. The motivation to use a neural network is provided in the statement by Ioannidis et al., which says, "neural networks could be trained to recognize genetic patterns in conjunction with associated clinical outcomes, and their performance in modeling these complex associations in a training set was superior to logistic regression models (page 469, column 1)". Harrigan et al. use logistic regression in their assessment of baseline resistance, however, it would have been obvious to improve the accuracy of the resistance testing by using the neural network of Ioannidis et al. for the reasons set forth above.

No claims are allowed.

Inquiries

Papers related to this application may be submitted to Technical Center 1600 by facsimile transmission. Papers should be faxed to Technical Center 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notices published in the Official Gazette, 1096 OG 30 (November 15, 1988), 1156 OG 61 (November 16, 1993), and 1157 OG 94 (December 28, 1993) (See 37 CFR § 1.6(d)). The CM1 Fax Center number is either (703) 308-4242, or (703) 308-4028.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lori A. Clow, Ph.D., whose telephone number is (571) 272-0715. The examiner can normally be reached on Monday-Friday from 10 am to 6:30 pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael P. Woodward, Ph.D., can be reached on (571) 272-0722.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

MARJORIE MORAN
PATENT EXAMINER

August 9, 2004
Lori A. Clow, Ph.D.
Art Unit 1631